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THE
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TREATMENT OF EXTERNAL OTITIS.

III — THE USE OF VEHICLES AND ANTIBIOTICS IN THE EXTERNAL AUDITORY CANAL. IN VITRO STUDIES.*

BEN H. SENTURIA, M.D., and JOHN A. DOUBLY, M.S.,
St. Louis, Mo.

INTRODUCTION.

Topical therapy of external otitis has been effective in most cases but has failed to produce the desired results in others. Among many possible explanations for success or failure of therapy one must consider the nature and activity of the vehicle in which the therapeutic agent is incorporated.

The study herein reported was undertaken to gather the available literature on the functions and properties of vehicles used in the external ear and to evaluate these characteristics as they influence the action of therapeutic agents used in the treatment of infections involving the external auditory canal and tympanic membrane.

It has been demonstrated that a typical bacteriological and mycological flora may be obtained from cultures of the normal external auditory canal.[1,2,3,4,5] A consistent distribution of organisms is found if infections of the ear canal are classified into various categories. Invariably Gram positive organisms may be cultured from circumscribed lesions, while diffuse lesions more often show Gram negative bacilli, only occasionally Gram positive organisms, and frequently a mix-

*From Department of Otolaryngology, Washington University School of Medicine, St. Louis, Mo.

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ture of the two. In a small percentage of cases, so-called saprophytic fungi have been cultured from lesions of the external ear canal.[1,2,3,6,7,8,9]

With the introduction of penicillin, streptomycin and various sulfonamides, reports have appeared in which these medications were applied directly to the surface of the infected skin of the ear canal.[10,11,12] Streptomycin and penicillin were incorporated in a vehicle and used for topical application while powdered sulfonamides were dusted directly into the canal. It was shown that penicillin, in an aqueous carrier, may be of value when applied to circumscribed or diffuse lesions in which Gram positive organisms were found.[11] Equivocal results were obtained when penicillin-sulfonamide powder was applied to the ear canal. A mixture of sulfanilamide, sulfathiazole and zinc peroxide powder (4:1:1) gave satisfactory results.[10] When streptomycin was used in adequate concentration, and incorporated in a "carboprop" vehicle it was shown to be effective in eliminating Gram negative bacilli from the ear canal.[12]

The response to sulfonamide therapy and antibiotics was excellent in some cases but failed in others. Because the success or failure of this therapy may be the nature of the vehicle in which the agent was incorporated, it was considered desirable to define, classify and evaluate the action of vehicles as they affect therapy.

DEFINITION AND CLASSIFICATION OF VEHICLES.

For purposes of this study a vehicle may be defined as a liquid or semisolid substance which acts as a carrier or reservoir for a therapeutic agent or drug. It is usually without specific therapeutic action but may have a physicochemical action upon the skin.

As pointed out by Lane and Blank in their comprehensive treatise on this subject,[13] one must carefully consider the functions performed by and the physicochemical properties of any vehicle under consideration. Excellent reviews of this subject have appeared in the literature.[14,15,16,17,18,19]

Some of the more important physical and physicochemical properties of vehicles are: *1.* volatility, *2.* viscosity, *3.* water solubility, and *4.* compatibility and miscibility with therapeutic agents. More essential, however, are some functions of vehicles which are of importance in therapy of the external auditory canal. These may be listed as follows: *1.* the vehicle acts as a carrier and reservoir of therapeutic agents, *2.* it protects the skin, *3.* it aids in the removal of cutaneous secretions, and *4.* it influences the penetration of a drug into the skin.

On the basis of these physicochemical properties and functions, the following vehicles have come into popular use in otology and will be considered in this report:

LIQUIDS	SEMISOLIDS
Water	Vaseline
Ethyl alcohol	Hydrous lanolin
Glycerin	Anhydrous lanolin
Propylene glycol	Carbowax*
Olive oil	Hydrosorb†
Castor oil	Aquaphor‡
Mineral oil	Carboprop§

ACTION OF VEHICLES AS AFFECTING THERAPY.

In order to effectively apply the newer chemotherapeutic agents or antibiotics to the ear canal they must be incorporated into vehicles. It would be desirable, therefore, to know how the vehicle influences the activity of the agent. What effect does the vehicle have upon the activity of the incorporated therapeutic agent? Does the vehicle permit transfer of the agent to the tissues? Does the vehicle facilitate penetration of the agent into the tissues? What effect does the vehicle have upon the skin of the ear canal and how does it

*Mixtures of high molecular weight polyethylene glycols, products of Carbide Carbon Chemical Corp., New York, N. Y.

†Consists of oleic acid esters, amide of diethanolamine, oleic acid and white petrolatum, a product of Abbott Laboratories, North Chicago, Ill.

‡An aliphatic hydrocarbon base consisting of 6% of a group of esters of cholesterol, a product of Duke Laboratories, Stamford, Conn.

§A mixture of carbowax (4000) 60% and propylene glycol 40%.

react with the secretions of the skin appendages peculiar to the canal?

I.—Effect of the Vehicle on the Therapeutic Agent.

The effect of various vehicles on the antibacterial action of streptomycin and penicillin has not been extensively investigated. It has been shown that carbowax-propylene glycol mixtures apparently did not inhibit the in vitro antibacterial action of penicillin, while propylene glycol alone either inhibited or destroyed penicillin activity.[20] Although aquaphor markedly interfered with the antibacterial action of penicillin,[21] the use of increasing amounts of water in the vehicle reduced this inhibitory effect.

The effect of vehicles upon the antibacterial action of streptomycin-penicillin mixtures is of interest. Such mixtures have a broader potential antibacterial spectrum and may have increased activity against a given strain of organism. Many investigators[22,23,24,25,26] have observed in vitro and in vivo that combinations of the sulfonamides with various antibiotics have an antibacterial effect that was greater than the effect of either alone. Relatively few observations have been made on the increased antibacterial action of mixtures of antibiotics. Foster and Woodruff[27] found that streptothricin plus penicillin gave a combined antibacterial effect in vitro which was almost quantitatively the sum of the antibacterial action of either one alone. Heilman and Herrel[28] found the in vitro antibacterial action of gramicidin and penicillin was only slightly increased.

II.—Transferability of Therapeutic Agents from Vehicles.

In order for an agent to exert a chemical or physiologic effect on the skin, it must be transferred from the vehicle to the surface of the skin. This transfer depends first on the miscibility of the vehicle with the substances on the skin surfaces, and second on the relative solubility of the agent in the vehicle and in the skin secretions. With few exceptions a vehicle will be miscible only with skin secretions or exudates having similar characteristics. Thus an aqueous

vehicle will mix easily with sweat but will not mix readily with fatty sebaceous secretions. Petrolatum will mix with a fatty film but will not mix with sweat. Lanolin will mix with both oily and aqueous surface films.

In vitro studies with antiseptics have shown that many vehicles tend to hold or bind the agent and prevent its diffusion. Some years ago it was observed that vegetable oils inhibited the germicidal action of phenol.[29] Later, it was shown[30,31] that as an ointment was made a better solvent for an antiseptic, its antiseptic value decreased; thus many vehicles tend to hold or bind the therapeutic agent and prevent its diffusion into the tissues. This property of diffusion is in accordance with the partition law, which states that an agent will distribute itself between two immiscible solvents in direct proportion to its relative solubility in the two solvents.[32]

III.—Penetration of Vehicles.

Considerable research has been performed on the penetration of vehicles into the skin.[33,34,35,36,37] It has been observed that those vehicles which penetrate the skin do so along the hair follicles and into the sebaceous gland ducts. There is no penetration directly through the epidermis, although diffusion into the upper loose layer of stratum carneum does occasionally occur. These workers have also found that mineral vehicles such as vaseline and petroleum jelly do not "penetrate the skin" as well as do animal fats (*e.g.*, lanolin or lard) or vegetable oils (*e.g.*, olive oil).[33,34] It has also been shown that the use of synthetic detergents with ointment bases greatly increases its penetrability into sebaceous glands.[38] Preparations of an aqueous vehicle containing a synthetic detergent and tyrothricin gave favorable clinical response in various skin diseases caused by pyogenic infections.[39] On the other hand, it has been shown that the antibacterial action of certain antibiotics may be hindered by synthetic detergents. Thus the antibacterial properties of gramicidin were inhibited by phemerol* while the activity of penicillin was not interfered with by either phemerol or zephiran.†[40]

*Alkyl dimethyl benzyl ammonium chloride (alkyl = para-tertiary-octyl-phenyl-diethoxy).

†Mixture of alkyl dimethyl benzyl ammonium chlorides (alkyl = C_8 to C_{18}).

IV.—Action of the Vehicle on Ear Wax.

As a preliminary to effective topical application of therapeutic agents, it is necessary to remove cerumen from the external ear canal. The presence of cerumen, a solid wax-like organic material, may interfere with the action of therapeutic materials by acting as a protective film or barrier. It is an established fact that organic matter markedly reduces the effectiveness of germicidal and antiseptic substances;[41] furthermore, it has been shown that cerumen[6,42] as well as sweat[43] will support the growth of some microorganisms. Thus there is a twofold purpose in removing cerumen from the ear canal preliminary to treatment; namely, elimination of a substance that may interfere with effective therapy and removal of media which may serve as a potential nutritive source for the growth of infecting organisms.

In order to facilitate removal of cerumen, some knowledge of its composition is desirable. Cerumen is a complex composite of the secretions of the sebaceous glands, modified sweat glands and exfoliated scales of epithelium and hair filaments from the skin of the external ear canal. If we examine these constituents, we learn that sebum is composed of approximately 32 per cent water, 62 per cent protein matter, 5 per cent fats and fatty acids, and 1 per cent ash.[44] Sweat contains approximately 99 per cent water, 1 per cent sodium chloride, and traces of fatty acids such as acetic, propionic, caprylic and caproic acids.*[45,46] The substances derived from the skin are mainly protein keratin, oleic acid, cholesterol, lecithin, cephalin, inorganic salts, sodium chloride and dextrose.[47,48]

Apparently the largest part of the water contained in these secretions is quickly lost. According to Gautier,[44] the complex chemical substance which remains and which we term cerumen is composed mainly of 10 per cent water, 26 per cent fatty material, 52 per cent potassium soaps, 12 per cent organic matter and traces of calcium and sodium.

*These are constituents of body sweat. Analysis of the secretions of the modified sweat glands of the ear canal is not available.

In order to soften or remove this material from the ear canal many substances have been suggested. Among these may be listed hydrogen peroxide, mineral oil, olive oil, glycerin alone or with 4 per cent sodium bicarbonate or with phenol and sodium borate, 5 per cent sodium carbonate in 50 per cent glycerin and 50 per cent water, and acidolate.*[49,50]

METHODS.

The antibiotics, streptomycin† and penicillin,‡ were studied because of their reputed potency against certain types of bacteria usually encountered in external ear infections[1,51,52] Streptomycin was used in a concentration of 5 mg. per gm. or cc., and penicillin in a concentration of 1,000 and 2,000 units per gm. or cc.

Test preparations of the antibiotics in the different vehicles were made by incorporating appropriate aqueous concentrates of the antibiotics into the different vehicles so that the required final concentration of each was obtained.

The test organisms included a penicillin and streptomycin-sensitive strain of staphylococcus aureus, and a streptomycin-sensitive but penicillin-insensitive strain of pseudomonas; both had been isolated from cases of acute external otitis.

The F.D.A. agar cup-plate technique[45] was utilized to study the influence of vehicles on the antibacterial action of streptomycin and penicillin. This method consisted of inoculating a 24-hour broth culture of the test organism into melted agar at a pH of 7.2 cooled to 55° C. Fifteen to 20 cc. of the agar was poured into sterile Petri plates and allowed to solidify. A well or cup 1.5 cm. in diameter was cut in the center of each plate with a suitable instrument and the plug of agar removed. The bottom of the cup so formed was sealed with a drop or two of melted agar. The cup was filled with test material and the plates incubated at 37° C. The results were

*Acidolate—a mixture of 25 per cent sulfonated mixed olive and teaseed oils, 25 per cent liquid petrolatum and 50 per cent water. Manufactured by National Oil Products Co., Harrison, N. J.

†Streptomycin—C.S.C. sulfate—Commercial Solvents Corp., Terre Haute, Ind.

‡Penicillin Sodium Squibb—E. R. Squibb & Sons, New York, N. Y.

read after 24 and 48 hours. If the preparation had an inhibiting effect on the inoculated strain of organisms there was a clear circular area about the cup in which bacteria did not grow and an outer circular area which appeared cloudy, due to partial inhibition of bacterial growth. The remainder of the plate was opaque as a result of uninhibited growth of the test organism. Eight measurements around the cup were made of the radius of the zone of inhibition, *i.e.*, from the outer rim of the cup to the farthest point of complete inhibition of bacterial growth, and averages calculated for each test material. Diffusion of the agent from the vehicle into the agar medium was rated in the following manner:

MEASUREMENTS OF INHIBITION (AVERAGE IN MM.)	Rating
0 to 1.0 mm.	0
1.0 to 3.0 mm.	1+
3.0 to 5.0 mm.	2+
5.0 to 7.0 mm.	3+
7.0 to 10.0 mm.	4+

Tests on the combined effect of streptomycin and penicillin in various vehicles were performed using dilution and agar cup techniques. The dilution technique was carried out by adding 0.1 cc. of diminishing concentrations of streptomycin and penicillin, and streptomycin-penicillin mixtures to a series of cotton-plugged sterile tubes, each containing 0.9 cc. of beef broth at pH 7.2. The initial concentration of streptomycin was 5.0 mg. per cc., that of penicillin, 1,000 units per cc. Each tube was inoculated with 0.02 cc. of a 24-hour broth culture of a sensitive strain of staphylococcus aureus, and the tubes were then incubated for 24 and 48 hours at 37° C. The results were read for the presence or absence of growth.

The transfer of agents from vehicles was tested by incorporating various concentrations of cresatin and thymol in different vehicles and determining the diffusion of these preparations by a modified agar cup-plate technique. Sabouraud's agar was used as the test medium. The agar was melted and cooled to 55° C. and inoculated with a spore suspension of either A. niger, A. fumigatus or C. albicans prepared by add-

ing 10 cc. of broth to a seven-day Sabouraud agar slant and 1 cc. of the suspension was added to each 100 cc. of melted agar. Fifteen to 20 cc. of the inoculated agar was poured into sterile Petri plates, allowed to solidify, and cups made. The test material was added to the cups and the prepared plates incubated at 37° C. for 48 hours and the results recorded.

The effect of the detergents zephiran, phemerol, duponal C* and aerosol† upon the antibacterial action of streptomycin and penicillin was determined by dilution and agar cup techniques using two strains of staphylococcus aureus and two of pseudomonas (sp).

In order to observe the action of various vehicles upon cerumen obtained from normal subjects, 1 cc. of various test preparations was added to approximately 0.5 gm. of cerumen placed in the bottom of a small diameter vial. The vials were allowed to stand at room temperature without agitation for periods of 5, 10, 15, 30, 60 minutes and 24 hours. Notations were made of the time required to produce an observable effect on the ear wax and the type of action, such as softening, dissolving, disintegration and swelling.

RESULTS.

I.—The Effect of the Vehicle on Action of the Agent.

The effect of the vehicle on the in vitro activity of streptomycin and penicillin was studied by the agar cup-plate method. The activity of streptomycin incorporated in various vehicles is shown in Table 1. Effective in vitro antibacterial activity was obtained with the water soluble vehicles such as glycerin, carbowax, and mixtures of carbowax and propylene glycol. On the other hand, the water insoluble vehicles such as lanolin, aquaphor and hydrosorb showed little or no in vitro antibacterial action of the contained antibiotic. Propylene glycol was not tested with streptomycin because a precipitate was formed on admixture.

The influence of the vehicle on the action of penicillin was

*Sodium alkyl sulfates (principally lauryl).
†Di octyl sodium sulfo succinate.

similar to the effects observed with streptomycin (see Table 2). The water insoluble vehicles interfered with the antibacterial action of penicillin, while the water soluble vehicles

TABLE 1. EFFECT OF VEHICLES ON THE ANTIBACTERIAL ACTION OF STREPTOMYCIN USING THE AGAR-CUP TECHNIQUE.

Preparation	Rating of Inhibition Staph. Aureus	Pseudomonas (sp)
Streptomycin 5.0 mgm. per cc. of distilled water	4+	4+
Streptomycin 5.0 mgm. per gram of glycerin U.S.P.	4+	4+
Streptomycin 5.0 mgm. per gram of carbowax 4000	4+	4+
Streptomycin 5.0 mgm. per gram of "carboprop"	4+	4+
Streptomycin 5.0 mgm. per gram of lanolin U.S.P. (anhydrous)	0	0
Streptomycin 5.0 mgm. per gram of lanolin U.S.P. (hydrous)	0	0
Streptomycin 5.0 mgm. per gram of aquaphor	0	0
Streptomycin 5.0 mgm. per gram of hydrosorb	0	0

TABLE 2. EFFECT OF VEHICLES ON ANTIBACTERIAL ACTION OF PENICILLIN USING THE AGAR-CUP TECHNIQUE.

Preparation	Rating of Inhibition Staph. Aureus	Pseudomonas (sp)
Penicillin 1,000 units per cc. of distilled water	2+	0
Penicillin 1,000 units per gram of glycerin U.S.P.	2+	0
Penicillin 1,000 units per gram of propylene glycol	0	0
Penicillin 1,000 units per gram of carbowax 4000	2+	0
Penicillin 1,000 units per gram of carbowax 1500	1+	0
Penicillin 1,000 units per gram of "carboprop"	2+	0
Penicillin 1,000 units per gram of lanolin U.S.P. (anhydrous)	0	0
Penicillin 1,000 units per gram of lanolin U.S.P. (hydrous)	0	0
Penicillin 1,000 units per gram of aquaphor	0	0
Penicillin 1,000 units per gram of hydrosorb	0	0
Distilled water	0	0
Glycerin U.S.P.	0	0
Propylene glycol	0	0
Lanolin U.S.P. (anhydrous)	0	0
Lanolin U.S.P. (hydrous)	0	0
Aquaphor	0	0
Hydrosorb	0	0
Carbowax 4000	0	0
Carbowax 1500	0	0
"Carboprop"	0	0

did not show such activity. Propylene glycol, which is water soluble, was one exception since it completely inhibited or destroyed the in vitro antibacterial action of penicillin. This

effect, however, was not apparent when propylene glycol was compounded with carbowax. None of the vehicles alone showed antibacterial action against staphylococcus or pseudomonas.

The action of vehicles on streptomycin-penicillin mixtures using the agar cup method is shown in Table 3. In distilled

TABLE 3. EFFECT OF VEHICLES ON ANTIBACTERIAL ACTION OF STREPTOMYCIN-PENICILLIN MIXTURES USING THE AGAR-CUP TECHNIQUE

Preparation	Rating of Inhibition Staph. Aureus	Pseudomonas(sp)
Streptomycin 5.0 mgm. per cc. of distilled water	4+	4+
Penicillin 1,000 units per cc. of distilled water	2+	0
Streptomycin 5.0 mgm. per cc. and penicillin 1,000 units per cc. of distilled water	4+	4+
Streptomycin 5.0 mgm. per cc., penicillin 1,000 units per cc. and zephiran 0.1% in distilled water	4+	4+
Streptomycin 5.0 mgm. per gram and penicillin 1,000 units per gram of "carboprop"	3+	4+
Streptomycin 5.0 mgm. per gram and penicillin 1,000 units per gram of hydrosorb	1+	1+
Streptomycin 5.0 mgm. per gram and penicillin 1,000 units per gram of lanolin U.S.P. (hydrous)	0	0
Streptomycin 5.0 mgm. per gram and penicillin 1,000 units per gram of aquaphor	0	0

water, the mixture showed no greater antibacterial action than streptomycin without added penicillin. The streptomycin-penicillin mixtures incorporated in "carboprop" showed a slight diminution of antibacterial action against staphylococcus aureus, but no loss against pseudomonas as compared with the activity of the mixture in distilled water. Streptomycin-penicillin mixtures in hydrosorb showed slight activity against both test organisms; however, when the mixtures were incorporated in hydrous lanolin and in aquaphor, there was complete inhibition of antibacterial action.

The results of tests on the antibacterial action of streptomycin, penicillin and streptomycin-penicillin mixtures on staphylococcus aureus by the broth dilution method are seen in Table 4. Streptomycin in a concentration of 0.05 mg. per cc. inhibited the growth of the test organism for 48 hours. Penicillin in a concentration of 100 units per cc. inhibited

growth of staphylococcus aureus for 24 hours, but not for 48 hours. It required 1,000 units per cc. of penicillin to be completely inhibitory to the growth of the staphylococcus over a period of 48 hours. In sharp contrast, streptomycin, in a concentration of 0.0005 mg. per cc. with 0.1 unit per cc. of penicillin showed complete inhibition of growth of the test organism in both 24 and 48 hours. Thus streptomycin-penicillin mixtures had an antibacterial action that was far greater than the action of each alone.

TABLE 4. ANTIBACTERIAL ACTION OF STREPTOMYCIN-PENICILLIN MIXTURES ON STAPH. AUREUS USING A BROTH DILUTION TECHNIQUE.

Antibiotic	Concentrations per cc. of Broth						
Streptomycin (mg/cc)	5.0	0.5	0.05	0.005	0.0005	0.00005	0.000005
24 hours' incubation	—	—	—	+	+	+	+
48 hours' incubation	—	—	—	+	+	+	+
Penicillin (units/cc)	2,000	200	20	2	0.2	0.02	0.002
24 hours' incubation	—	—	+	+	+	+	+
48 hours' incubation	—	+	+	+	+	+	+
Streptomycin (mg/cc) and	5.0	0.5	0.05	0.005	0.0005	0.00005	0.000005
Penicillin (units/cc)	2,000	200	20	2	0.2	0.02	0.002
24 hours' incubation	—	—	—	—	—	+	+
48 hours' incubation	—	—	—	—	—	+	+

Legend: (+) growth of Staph. aureus.
(—) no growth of Staph. aureus.

II.—Transferability of Therapeutic Agents from Vehicles.

The inhibitory action of thymol and cresatin incorporated in several vehicles was tested against three strains of fungi isolated from cases of otomycosis. The results as seen in Table 5 reveal that cresatin alone, in ethyl alcohol, and in the various oils, had excellent inhibitory activity against A. niger, A. fumigatus and C. albicans. This fungicide was still very active when reduced to a 25 per cent concentration, and slight activity against A. niger was still present when the concentration of cresatin in an olive oil vehicle was dropped to 5 per cent.

The results with thymol are in sharp contrast. When dissolved in ethyl alcohol (70 and 95 per cent), 2 per cent thymol showed inhibitory activity against the three strains of fungi

tested, but no inhibition occurred when thymol was incorporated in olive oil, castor oil, corn oil or mineral oil. No fungistatic activity of the vehicles alone was noted.

TABLE 5. EFFECT OF VEHICLES ON THE TRANSFERABILITY OF THERAPEUTIC AGENTS USING A MODIFIED AGAR-CUP TECHNIQUE

Preparation	Inhibition of Growth of Fungi		
	A. niger	A. fumigatus	C. albicans
Cresatin 100%	Complete	Complete	Complete
Cresatin 25% in ethyl alcohol 95%	Complete	Complete	Complete
Cresatin 10% in ethyl alcohol 70%	Complete	(—)	(—)
Cresatin 50% in olive oil	Complete	Complete	Complete
Cresatin 10% in olive oil	Partial	(—)	(—)
Cresatin 5% in olive oil	Slight	(—)	(—)
Cresatin 50% in corn oil	Complete	(—)	(—)
Cresatin 50% in castor oil	Complete	(—)	(—)
Thymol 10% in ethyl alcohol 95%	Complete	(—)	(—)
Thymol 2% in ethyl alcohol 95%	Partial	Complete	Complete
Thymol 2% in ethyl alcohol 70%	Complete	(—)	(—)
Thymol 1% in ethyl alcohol 70%	Partial	(—)	(—)
Thymol 10% in olive oil	None	(—)	(—)
Thymol 2% in olive oil	None	None	None
Thymol 1% in olive oil	None	None	None
Thymol 2% in castor oil	None	(—)	(—)
Thymol 2% in corn oil	None	(—)	(—)
Thymol 2% in mineral oil	None	(—)	(—)
Ethyl alcohol 95%	None	None	None
Ethyl alcohol 70%	None	None	None
Olive oil	None	None	None
Castor oil	None	None	None
Corn oil	None	None	None
Mineral oil	None	None	None

Legend: (—) not tested.

It should be pointed out that 10 per cent cresatin in 70 per cent ethyl alcohol caused complete inhibition of fungus growth, while the same concentration of the agent in olive oil gave only partial inhibitory activity; thus it appears that the oily vehicles bind cresatin as well as thymol, but the intense fungistatic activity of the former allows for satisfactory in vitro inhibition of the tested organisms.

III.—Penetration of Vehicles.

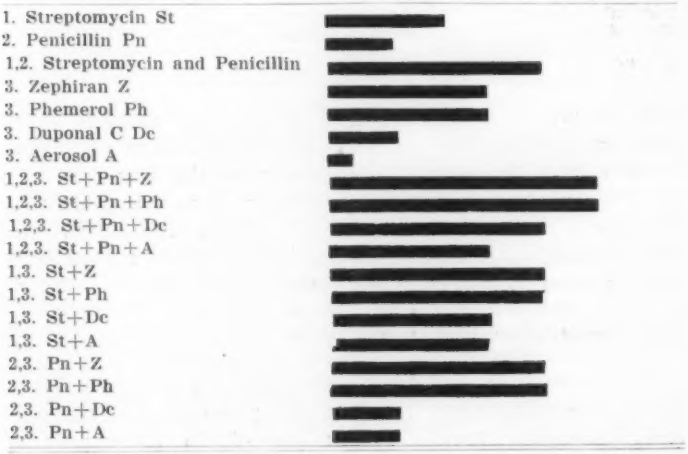
The results seen in Table 6 and Charts I and II reveal that the cationic detergents, zephiran and phemerol, and the anionic detergents, duponal C and aerosol, do not appear to

TABLE 6. EFFECT OF SYNTHETIC DETERGENT UPON THE ANTIBACTERIAL ACTION OF STREPTOMYCIN AND PENICILLIN USING THE AGAR-CUP TECHNIQUE.

Preparation	Rating of Inhibition Staph. aureus	Pseudo-monas (sp
Streptomycin 5.0 mgm. per cc. of distilled water	4+	4+
Penicillin 1,000 units per cc. of distilled water	2+	0
Zephiran 0.1% in distilled water	3+	0
Streptomycin 5.0 mgm. per cc. and zephiran 0.1% in distilled water	4+	4+
Penicillin 1,000 units per cc. and zephiran 0.1% in distilled water	3+	0
Distilled water	0	0

CHART I. CONCENTRATIONS OF DETERGENTS AND ANTIBIOTICS WHICH INHIBIT THE GROWTH OF STAPHYLOCOCCUS AUREUS.

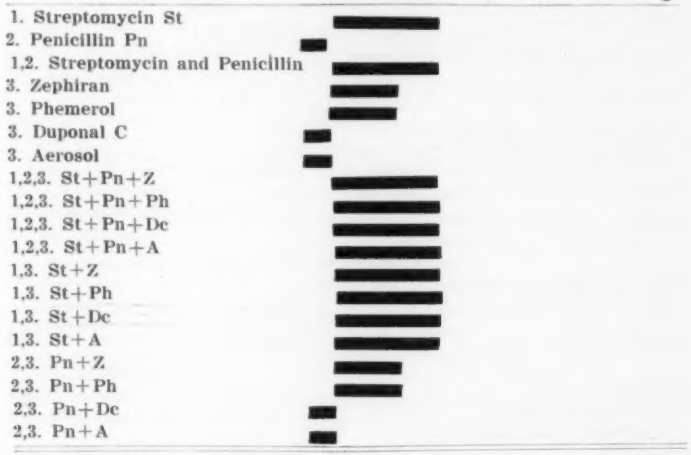
1. Streptomycin mgm. per cc.	5.0	0.5	0.05	0.005	0.0005	0.00005	0.000005
2. Penicillin units per cc.	2,000	200	20	2.0	0.2	0.02	0.002
3. Detergents mgm. per cc.	1.0	0.1	0.01	0.001	0.0001	0.00001	0.000001



inhibit the antibacterial activity of streptomycin,* penicillin or mixtures of streptomycin and penicillin against staphylococcus and pseudomonas (sp). The effect of these detergents

CHART II. CONCENTRATIONS OF DETERGENTS AND ANTIBIOTICS WHICH INHIBIT THE GROWTH OF PSEUDOMONAS (SP).

1. Streptomycin mgm. per cc.	5.0	0.5	0.05	0.005	0.0005	0.00005	0.000005
2. Penicillin units per cc.	2,000	200	20	2.0	0.2	0.02	0.002
3. Detergents mgm. per cc.	1.0	0.1	0.01	0.001	0.0001	0.00001	0.000005



on penicillin is not apparent when pseudomonas (sp) is used as the test organism because penicillin 2,000 units per cc. shows no inhibitory action against this organism; furthermore, there was no increase in antibacterial action of penicillin-zephiran and penicillin-phemerol as compared to zephiran alone and phemerol alone.

*Streptomycin hydrochloride—Merck & Co., Inc., Rahway, N. J.—was used in these experiments.

IV.—Effect of Vehicles and Therapeutic Preparations on Cerumen.

On a strictly qualitative basis it was observed, in vitro, that different vehicles vary in their action on cerumen removed from the human ear canal. The results in Table 7 reveal that

TABLE 7. IN VITRO ACTION OF VARIOUS VEHICLES AND THERAPEUTIC PREPARATIONS UPON CERUMEN.

Preparation	Action on Cerumen 5 Minutes	60 Minutes	24 Hours
Hydrogen peroxide 3.0%	Immediate action	Complete disintegration	
Hydrogen peroxide 1.5%	Immediate action	Complete disintegration	
Distilled water	Immediate action	Complete disintegration	
Saline 1% solution	Immediate action	Complete disintegration	
Saline 2% solution	Immediate action	Complete disintegration	
Ethyl alcohol 95%	No action	No action	Slight disintegration
Hydrochloric acid N/1	No action	No action	Slight disintegration
Sodium bircarbonate 1.5% solution	No action	Slow disintegration	Approx. ½ disintegrated
Sodium hydroxide N/1	No action	Slow disintegration	Approx. ½ disintegrated
Sodium carbonate 1.5% solution	Slight disintegration	Approx. ½ disintegrated	Approx. ¾ disintegrated
Sodium carbonate 5.0% in 50% glycerin	Slight disintegration	Slight disintegration	Complete disintegration
Acidolate	No action	No action	Surface softened and approx. ¼ dissolved
Glycerin	No action	No action	Surface softening
Glycerin with 0.1% zephiran	No action	No action	Surface softening
Auralgan	No action	No action	Surface softening
Otosmosan	No action	No action	Surface softening
Mineral oil	No action	No action	No action
Castor oil	No action	No action	No action
Propylene glycol	Slight swelling	Swelling	Pronounced swelling. No disintegration

distilled water, hydrogen peroxide (1.5 and 3 per cent), and saline solutions (1 and 2 per cent) showed immediate reaction with the cerumen and total disintegration occurred in 60

minutes. A much slower rate of disintegration was seen with aqueous preparations of sodium bicarbonate (1 and 1.5 per cent), sodium hydroxide (4 per cent), sodium carbonate (1.5 per cent) and sodium carbonate (5 per cent) in 50 per cent glycerin. In most tests with these alkaline solutions, there was little or no action in five minutes or 60 minutes, but one-half to three-fourths of each piece of cerumen was disintegrated in 24 hours. Ethyl alcohol (95 per cent) and normal hydrochloric acid showed very little action in 24 hours.

The oily preparations did not show any disintegrating effect. Acidolate showed a surface softening and a slight dissolving action in 24 hours. Glycerin, glycerin with zephiran (0.1 per cent), auralgan, and otosmosan showed only surface softening, while mineral oil and castor oil had little effect after 24 hours. Propylene glycol showed an immediate swelling action on cerumen without any apparent softening effect.

DISCUSSION.

The data presented here reveal that the physical and chemical properties of vehicles may, to a great measure, determine the success or failure of any specific treatment applied to the external ear.

Although the primary function of a vehicle is to hold and carry a therapeutic agent, it is frequently observed that some physical or chemical characteristic of the vehicle may completely inhibit the activity of that agent. In this regard the in vitro findings indicate that streptomycin and penicillin should not be incorporated into water insoluble vehicles such as lanolin, although complete activity is maintained in water soluble vehicles such as glycerin.

There has been some pharmaceutical tendency to substitute propylene glycol for glycerin as a carrier of therapeutic agents. For various reasons it might appear desirable to incorporate streptomycin or penicillin, or both, in propylene glycol for ready application to the ear canal and tympanic membrane. It is important, therefore, to note that streptomycin and propylene glycol are incompatible and the latter

inhibits the in vitro activity of penicillin despite its water solubility.

When streptomycin is incorporated into carbowax or carbowax-propylene glycol preparations, in vitro activity is retained. These observations on the antibacterial activity of streptomycin in carbowax mixtures are confirmed in vivo in a previous report[12] in which successful treatment of infected ear canals with streptomycin in "carboprop" was accompanied by a rapid disappearance of pseudomonas (sp) from the infected ear canal.

When penicillin is compounded with propylene glycol and carbowax (1500), there is a marked reduction of antibacterial action. On the other hand, carbowax (4000) and "carboprop" mixtures showed no such inhibitory activity. These findings are in agreement with the extensive in vitro findings of Meleney and Johnson.[20,54]

When streptomycin and penicillin are incorporated in a vehicle, there may be an inhibitory action of the vehicle to one or both antibiotics or an interaction between the two antibiotics. This may interfere with or potentiate antibacterial action. These possibilities were investigated by two techniques, a broth dilution test and the agar cup test.

It is significant that the streptomycin-penicillin mixture, in a broth vehicle, showed a marked potentiating antibacterial effect against staphylococci. Although no such potentiation was observed with the less accurate agar cup test, it is important that no interference of streptomycin or penicillin activity occurred as a result of the mixture or the action of the vehicle.

Just as in the case of the individual therapeutic agents discussed above, the water miscible vehicles did not interfere with the antibacterial action of streptomycin-penicillin mixtures, while the water immiscible vehicles markedly inhibited their activity.

From the practical clinical point of view, the use of streptomycin-penicillin mixtures might result in a reduction of

the incidence of drug-fast strains of bacteria developing from the use of either antibiotic alone. Specific resistant mutant bacteria are normally present in every culture and may form the basis for a resistant strain of bacteria. Various investigators[55,26] have shown that bacterial resistance to streptomycin, penicillin and sulfonamides is drug specific. Klein and Kalter[26] have demonstrated that the increased antibacterial action of penicillin-sulfonamide mixtures over either agent alone is due to inhibition of growth of penicillin-resistant organisms by the added sulfonamide.

The potentiating antibacterial effect observed here with streptomycin-penicillin mixtures suggests that this combination of antibiotics eliminates the streptomycin or penicillin-resistant bacteria normally present in a culture, since all streptomycin and penicillin-resistant mutants present are usually sensitive to either one or the other antibiotic.[55]

The relationship of ear wax to external ear diseases and the influence of vehicles upon ear wax appear worthy of consideration. A study of this problem, however, will require a more complete understanding of the chemical constituents of cerumen. Only preliminary observations, therefore, were made of the action of various vehicles and therapeutic preparations upon ear wax.

It is of clinical significance that the simpler aqueous vehicles, *i.e.*, water, hydrogen peroxide and 2 per cent saline were most effective, in test tube experiments, in causing rapid and complete disintegration of the ceruminous mass. Despite the relatively large fat content in ear wax, these preparations softened and disintegrated the hard, waxy plugs. The effectiveness of these aqueous vehicles may be attributed to the high percentage of soaps found in cerumen. On the other hand, mineral oil, castor oil and glycerin showed little effect upon the ear wax except that of surface softening.

It would appear from these data that if the otologist desires rapid disintegration of an impacted ceruminous mass, ear drops containing an aqueous vehicle or solution such as normal saline would be effective. It is obvious, however, that the

wet semisolid debris thus formed would have to be removed by irrigation. On the other hand, if it is the purpose of the pediatrician or otologist to remove the wax with a curette, a vehicle such as glycerin would be more desirable in order to soften the surface of the impacted wax and thus facilitate mechanical removal.

It is worthy of particular note that the use of propylene glycol may be contraindicated in ears containing impacted cerumen. Rapid swelling of the ceruminous mass following the use of this vehicle might make removal more difficult and could conceivably cause severe pressure and pain.

The problem of the transfer of therapeutic agents from vehicle to tissues needs wider recognition. References in the literature may be found advising the use of various therapeutic agents in such vehicles as mineral oil and olive oil without consideration of their effect upon the agent. If the agent distributes itself so that it is more soluble in the vehicle than in the tissues, then a limited therapeutic effect will be obtained; thus castor oil may successfully compete with the tissues for thymol so that little thymol is available for fungicidal activity. On the other hand, if alcohol is used as a vehicle, there is no interference and excellent fungistatic activity is obtained.

Penetration of agents and vehicles into the skin forms a most recent and important phase of dermatologic research. Various synthetic detergents have been incorporated into skin preparations in order to facilitate penetration. If detergents are to be used in this manner, consideration must be given to the possible inhibiting action against streptomycin and penicillin. These preliminary observations indicate that zephiran, phemerol, duponal C and aerosol have no inhibitory action upon penicillin, streptomycin and streptomycin-penicillin mixtures. Although zephiran and phemerol in the concentrations used show only moderate antibacterial activity against the strains of pseudomonas tested, it is very active against staphylococci and other Gram positive organisms.[56] It may be possible, then, to take advantage of the detergent and antibac-

terial properties of such an agent where a combination of activities is desirable. On the other hand, it should be noted that phospholipids, which may be present in the ear canal, may interfere with the antibacterial action of both anionic and cationic detergents.[57]

SUMMARY AND CONCLUSIONS.

The functions and physicochemical properties of vehicles as they relate to otologic practice were discussed, particularly in regard to the treatment of external otitis. The following activity of vehicles was considered: *a.* action of the vehicles on therapeutic agents, *b.* transferability of therapeutic agents from vehicles, *c.* penetration of vehicles, and *d.* effect of vehicles and therapeutic preparations on cerumen.

In vitro studies of these actions showed:

a. Incorporation of streptomycin, penicillin or mixtures of streptomycin and penicillin into water insoluble vehicles (lanolin, aquaphor, hydrosorb) results in complete inhibition of the antibacterial action of these agents against staphylococcus aureus, and of streptomycin against pseudomonas (sp). When the antibiotics singly and together are incorporated into water soluble vehicles (glycerin, carbowax and "carboprop") no interference of antibacterial action occurred. Propylene glycol was an exception in that it completely inhibited the antibacterial action of penicillin and was incompatible with streptomycin.

b. When both streptomycin and penicillin were incorporated in an aqueous vehicle, a potentiating antibacterial effect was obtained against staphylococcus aureus. It would appear that streptomycin-penicillin mixtures may be of value for the treatment of mixed infections and for reducing the survival of streptomycin or penicillin-fast strains of bacteria.

c. Castor oil, olive oil, corn oil and mineral oil completely inhibited diffusion of fungicidal concentrations of 2 per cent thymol, while 70 and 95 per cent ethyl alcohol did not inhibit its action against A. niger, A. fumigatus and C. albicans. It

appeared that the oily vehicles interfered with the fungicidal activity of cresatin and thymol.

d. Synthetic detergents which may be of value in facilitating penetration of therapeutic agents into the skin do not interfere with the in vitro antibacterial properties of penicillin, streptomycin or streptomycin-penicillin mixtures.

e. Experiments to determine the effect of various preparations on cerumen revealed that water, 1 and 2 per cent saline, and hydrogen peroxide in 1.5 and 3 per cent concentrations, showed a rapid disintegrating effect upon ear wax. Alkaline preparations revealed only a slow and partial disintegrating action. Glycerin preparations and acidolate showed only a slow surface softening action, while castor oil had no disintegrating or softening effect. Propylene glycol caused an undesirable swelling of cerumen.

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THE USE OF ANTIBIOTICS IN THE TREATMENT OF BACTERIAL INFECTIONS.*†

W. BARRY WOOD, JR., M.D. (by invitation),
St. Louis, Mo.

As an internist I am not qualified to do more than outline the principles of the subject of "The Use of Antibiotics in the Treatment of Bacterial Infections." I am convinced, however, that it is extremely important for all who use antibiotics to understand their pharmacology; therefore, I shall devote most of my discussion to the pharmacology first of penicillin, and secondly of streptomycin.

CLINICAL USE OF PENICILLIN.

Concerning the clinical use of penicillin there are certain important facts with which I am sure all of you are familiar. I would like to review them quickly:

1. Penicillin is effective in the treatment of acute infections caused by most Gram-positive micro-organisms (particularly Gram-positive cocci) and by the meningococcus and gonococcus.

2. Penicillin is effective in the treatment of both early and late syphilis.

3. It will control such highly fatal diseases as pneumococcal meningitis, where the case fatality rate in untreated cases is close to 100 per cent.

4. Penicillin will cure many cases of subacute bacterial endocarditis.

5. It has been successfully used in such suppurative lesions as pneumococcal empyema, acute osteomyelitis and cavernous sinus thrombosis.

6. Penicillin is a relatively nontoxic drug.

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†From the Department of Medicine, Washington University School of Medicine, and the Barnes Hospital, St. Louis, Mo.

In spite of the effectiveness of penicillin as a therapeutic agent, it has at least two important limitations: the first of these is its ineffectiveness in the treatment of infections caused by Gram-negative bacilli; second, its very rapid excretion from the body.

PHARMACOLOGY OF PENICILLIN.

The proper use of penicillin in clinical medicine depends a great deal upon knowledge of the pharmacology of the drug. This fact was brought home to us very forcibly in our own department recently when a young boy, 14 years of age, was admitted to the hospital with pneumococcal meningitis. During the previous three weeks he had been treated for a middle ear infection and had received one injection of penicillin a *week*. He entered the hospital *in extremis* and died of the meningitis within a period of 24 hours. The physician who had prescribed the penicillin in this case obviously must have been unfamiliar with the pharmacology of the drug.

When penicillin is administered intravenously in a dose of 20,000 units, it causes an immediate rise in the penicillin blood level to approximately 0.6 units per cc. Because of the rapid excretion of the drug by the kidneys, the blood level begins to fall almost immediately, and measurable quantities of the drug remain in the blood for less than three hours. Within the first hour after injection approximately 40 per cent of the penicillin can be recovered in the urine. It is because of this very rapid excretion of the drug that penicillin must be administered at frequent intervals during both day and night, if a bacteriostatic concentration of the drug is to be maintained in the blood. When the drug is injected intramuscularly, the blood level curve is much the same, although its peak is slightly lower, and the excretion in the urine is not quite so rapid. The intramuscular route is the one most widely used today in medical therapy. Subcutaneous injection gives very low blood levels and, therefore, is seldom used.

When the dosage is increased to 40,000 units, the peak of the blood level curve is higher, and detectable quantities of

the drug remain in the blood stream a little longer. Even with the large doses little drug remains in the blood after three hours. Since most of the penicillin is eliminated in the urine, it is not surprising that the blood level curve is markedly influenced by renal function. When the latter is depressed, the drug tends to remain in the blood stream considerably longer than in the normal patient.

The foregoing remarks apply to the use of penicillin dissolved in saline solution, the common vehicle used in medical practice. When penicillin is prepared in a mixture of oil and beeswax ("P.O.B."), the drug is absorbed more slowly from the site of intramuscular injection, and an adequate blood level may be maintained for as long as 24 hours. The usual dosage employed is 300,000 units per injection. In severe infections it is dangerous to rely upon this treatment alone because the blood level attained is not very high; however, if during the first day of treatment, one gives 300,000 units and then repeats it at the end of 12 hours, the blood level is usually adequate. From then on, it may be necessary to give the drug only once a day. Penicillin in oil and beeswax has been found to be effective in the treatment of mild bacterial infections and is particularly advantageous in that it can be used in treating patients in the home.

Penicillin also may be given by mouth, but it must be emphasized that there are definite limitations to this method of administration. When given orally the drug is absorbed mainly from the upper part of the gastrointestinal tract; however, only 20 to 30 per cent of the ingested drug is absorbed. Although some of the penicillin ingested may be destroyed by the hydrochloric acid in the stomach, the relatively low blood levels obtained by oral therapy are due mainly to the relatively poor absorption. The use of alkaline or amphoteric vehicles does not greatly influence the effectiveness of oral penicillin. Since only 30 per cent of the drug is absorbed, it is necessary to give approximately five times the amount of penicillin given intramuscularly in order to obtain the same blood level. A level of approximately one unit per cc. may be attained by the ingestion of 100,000 units every

three hours. Penicillin should not be prescribed just before meals, because the drug passes through the duodenum more rapidly after the ingestion of food and is thus even less completely absorbed.

Systemic penicillin therapy alone should not always be relied upon. In the treatment of bacterial meningitis, for example, it is unwise to use only intravenous or intramuscular penicillin, because the antibiotic does not readily cross the blood-brain barrier. If, on the other hand, it is injected directly into the subarachnoid space, it remains in the spinal fluid in appreciable concentrations for more than 24 hours; thus, it is necessary to administer the drug intrathecally only once a day. Since penicillin is somewhat irritating to the meninges and will cause a cellular reaction in the spinal fluid when given in doses of 10,000 units, it is advisable to limit the size of the intrathecal dose. Twenty thousand units dissolved in 3 to 5 cc. of saline will be tolerated by most adults if given only once a day. Ten thousand units a day combined with systemic treatment have been found to be effective in all but the most fulminating cases of bacterial meningitis.

Penicillin may also be used locally at sites other than the subarachnoid space. Its injection into empyema cavities, for example, has made it possible to cure many cases of empyema without the use of surgical drainage. The effectiveness of penicillin in the treatment of empyema is due to the fact that a sufficient concentration of the drug may be maintained in the empyema cavity not only to stop the growth of the offending organisms but also to kill them outright. Penicillin differs from the sulfonamides in that when it is present in sufficient concentration (about 25 units per cc.), it is *bactericidal;* thus, local penicillin treatment may be highly effective in the treatment of localized suppurative lesions such as empyema and other abscesses.

STREPTOMYCIN.

Streptomycin is a drug which is probably not so important to otolaryngologists as is penicillin. It is effective against Gram-negative bacilli such as the colon bacillus, Friedlander's

bacillus, Hemophilus influenza and the organism that causes tularemia. I need not remind you that the latter organism is occasionally the cause of suppurative tonsillitis. Finally, streptomycin is active against the tubercle bacillus and has been found to be particularly effective in the treatment of tuberculosis of the larynx and trachea. Like penicillin, however, streptomycin has its limitations. It is ineffective in the treatment of typhoid fever and brucellosis, both of which are caused by Gram-negative bacilli.

Streptomycin is not so innocuous as is penicillin. For example, in large doses it will cause irritation of the kidneys and when administered over a long period of time it frequently leads to vertigo, nausea and sometimes rather severe vomiting. It not infrequently causes transient deafness and in some cases of tubercular meningitis it has caused permanent deafness. Prolonged use almost uniformly leads to an appreciable eosinophilia.

Streptomycin is available in crystalline form and, therefore, is standardized in grams or milligrams rather than in biological units. Since streptomycin units, however, are frequently referred to in medical literature, it is useful to remember that 1 gm. of the drug is equivalent to a million units. The drug is dispensed in a vial containing 1 gm. Four to 10 cc. of saline are injected directly into the vial, and the saline solution of the drug is injected intramuscularly every three to six hours. A total of 1 to 3 gm. a day is administered in the treatment of most infections.

PHARMACOLOGY OF STREPTOMYCIN.

The pharmacology of streptomycin is very much like that of penicillin except that streptomycin is not excreted quite so rapidly in the urine and is not absorbed at all from the gastrointestinal tract. Streptomycin remains in the blood somewhat longer than does penicillin and, therefore, may be administered at slightly longer intervals. Only about 10 per cent of the injected streptomycin is excreted in the urine in the first hour as compared to 40 per cent of the penicillin.

Streptomycin is rarely given intravenously since it is absorbed rapidly from the intramuscular site and sometimes causes reaction when given by the intravenous route.

OTHER PRINCIPLES OF ANTIBIOTIC THERAPY.

With this background of the pharmacology of penicillin and streptomycin, I close the discussion by touching upon four other points that are of particular importance in antibiotic therapy:

First, the use of bacteriological cultures should be emphasized. Obviously, since penicillin is effective mainly against Gram-positive organisms and not against Gram-negative bacilli it is essential to identify the causative agent. If the infection is caused by a Gram-negative bacillus, streptomycin, of course, rather than penicillin should be used. Ideally, one should not only identify the offending micro-organism but one should also determine its sensitivity to the appropriate antibiotic agent. Such sensitivity tests, however, can only be carried out in relatively large laboratories and are certainly not needed in every case.

Second, a word of warning should be given concerning local therapy with antibiotics. It is tempting to use all chemotherapeutic agents locally, but local therapy is universally ineffective except in certain closed cavities. Acute streptococcal tonsillitis, for example, cannot be adequately treated by the use of penicillin troches. Effective concentrations of penicillin cannot be maintained for long on the surface of the tonsils or pharynx because of the continual washing effect of the saliva; also, all of the offending streptococci are not on the surface of the tonsils; many of them are deep in the tonsillar tissues. It is dangerous to rely upon local therapy alone in the treatment of severe infections anywhere in the body. Experience has shown that in most instances the main reliance must be placed upon systemic chemotherapy.

Third, comment should be made concerning the duration of antibiotic treatment. When patients are treated for only 12 to 24 hours, relapse is all too frequent. Bacteriostasis must

be maintained for a long enough period of time to give the natural defenses of the body, particularly the phagocytic cells, an opportunity to destroy the offending bacterial agent. Penicillin and streptomycin in the concentrations usually attained with systemic therapy do not kill the bacteria but merely slow down or stop their multiplication. In most cases of moderate or severe bacterial infection it is necessary to continue antibiotic therapy for at least three or four days after the temperature has fallen to normal.

Finally, a word about dosage. Penicillin is such a nontoxic drug that one should always err on the side of giving too much rather than too little. Severe infections may require as much as 50,000 units of penicillin every two hours. It is particularly important to start treatment with a relatively large dose and to maintain a high dosage for at least a period of 24 hours. If an inadequate dose is employed at the outset, the infecting organisms may become drug-fast and thus complicate therapy immeasurably.

CONCLUSION.

The introduction of antibiotics in medical therapy has revolutionized the treatment of acute bacterial infections. Clinical experience has clearly demonstrated that penicillin and streptomycin, when properly used, are highly effective in a wide range of bacterial infections. The proper use of both of these new therapeutic agents depends primarily upon an understanding of their pharmacology.

CHANGING CONCEPTS OF SINUSITIS.*

F. JOHNSON PUTNEY, M.D.,
Philadelphia, Pa.

Our present concepts of nasal accessory sinus disease have developed because of better understanding of nasal physiology and the use of antibiotic and chemotherapeutic agents. Proetz[1] has contributed toward our knowledge of sinus physiology, and proper function is now the primary aim even though anatomic defects exist. The surgical treatment of sinusitis has largely been replaced by medical management, and the emphasis is on restoration rather than removal or destruction of diseased tissue. At times, surgical correction of anatomic abnormalities is necessary to insure proper function, but care should be exercised to preserve normal structure. The numerous sulfonamides and the several antibiotics have changed the treatment of sinusitis, and with the development of newer drugs greater therapeutic aids can be anticipated.

Formerly, a membrane once diseased was assumed to remain permanently diseased, and complete extirpation was considered necessary for cure. The prevailing opinion now is that functional improvement can be obtained by adequate ventilation, drainage and drug treatment. Van Alyea's[2] studies indicate that a diseased membrane can return to normal providing metaplasia has not taken place. A membrane so restored is superior to the fibrous membrane that replaces the original membrane after its extirpation. When the pathologic change is irreversible. surgery is required, conservative operations usually being employed.

Sinusitis must be considered from an etiologic basis, including bacteriologic, pathologic and physiologic elements, to insure correct diagnosis and effective treatment. In general,

*From the Department of Laryngology and Bronchoesophagology, Jefferson Hospital, Philadelphia, Pa.

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allergic cases require primary attention to the allergic diathesis, those due to mechanical blockage of the ostia are relieved by simple surgical procedures, and acute bacterial sinusitis responds to penicillin by irrigation, aerosol introduction into the sinuses using negative pressure, or systemic means.

Certain notions regarding sinusitis have been discarded. Postnasal discharge does not necessarily mean sinusitis, for this is produced by a variable number of physiologic changes in the nose and sinuses resulting from improper diet or atmospheric ventilation, excessive smoking and drinking, or irritation. Significance can be attached to this complaint if the discharge is copious or purulent.

Nasal medications are not innocuous, and some produce chemical irritation. The use of nose drops over prolonged periods of time should be discouraged. The ideal nasal vasoconstrictor is nonirritating, does not inhibit ciliary action and approximates the pH of normal nasal secretion. It has been my experience that sulfonamide solutions, alone or in combination with vasoconstrictors, are alkaline, irritate the nasal and sinus mucosa, and may cause sulfonamide sensitivity in the individual.

Mass nasal suction is condemned, for any benefit is offset by the pronounced secondary reaction in the sinuses and about the ostia. Spot suction, using a small, straight cannula, removes masses of secretion without adding to the existing inflammation and edema.

ALLERGIC SINUSITIS.

The incidence of allergic factors producing sinusitis either singly or complicated by infection is high, and cases previously classed as hyperplastic are now regarded as allergic. Polyps, which originate chiefly from ethmoid cells but sometimes are found in the antra, suggest allergic disease, although the causative agent may be obscure.

In allergic sinusitis the common complaint is constant nasal discharge, which the patient usually describes as a

continual "cold," accompanied by nasal blockage, sneezing, coryza and itching about the eyes. In contrast to the typical pale and boggy appearance, the membrane may appear normal between attacks or during an attack of allergic activity be intensely inflamed, resembling an acute coryza. A high percentage of eosinophiles is frequently found in nasal smears, but an absence of eosinophiles does not exclude allergy.

In allergic conditions treatment is directed primarily toward the allergic diathesis, and when allergic factors are present the life and habits of the individual must be regulated accordingly. Active treatment consists of desensitization when sensitivity to specific excitants is found, and antihistamine drug therapy. Penicillin and the sulfonamides are of no value in uncomplicated allergic sinusitis but can be effectively used against secondary infections from sensitive organisms. Locally, shrinkage agents afford little benefit, but some relief may follow electrocoagulation or sclerosis of persistent inferior turbinate swelling. Operations upon the sinuses are not advisable, and unless they are necessary to eliminate uncontrollable infection little improvement results. Nasal polyps sometimes are eliminated when the general allergic state is controlled, but more often the polyps become organized, necessitating removal.

MECHANICAL SINUSITIS.

Mechanical sinusitis develops from interference with the ostia, which deflects the air currents and impedes ventilation and drainage. Chemical irritation from caustic vapors or unsuitable medication predisposes to secondary obstructive sinusitis. Anatomic blockage of one or more ostia by high septal deviations, polyps, enlarged and cystic turbinates, hematomas of the sinus membrane, and certain tumors, chiefly cysts and osteomas, may be responsible for this type of sinusitis. Aerosinusitis, with or without a hematoma in the membrane, occurs when an ostium is incompetent and air becomes trapped in the sinuses. Aerosinusitis is encountered mainly after sudden barometric pressure changes, as in rapid airplane descents. Long-standing obstruction predisposes to

stagnation of secretion, and subsequent bacterial invasion may lead to bacterial sinusitis.

In mechanical sinusitis the symptoms are similar to those of other forms of sinusitis, although the obstruction is rarely sufficient to impair nasal breathing. Pain with a feeling of pressure in the involved sinus develops when negative pressure is established.

Permanent nasal and sinus obstructions are treated surgically if there is encroachment on the ostia. Simple procedures, as infraction of an enlarged middle turbinate, removal of a few small polyps or submucous resection to unblock the middle meatus are followed by complete relief in many instances. Operation is not indicated in abnormalities not causing obstruction or impairing drainage. Aerosinusitis can usually be corrected by restoring proper nasal physiology through rest, heat and shrinkage.

BACTERIAL SINUSITIS.

Marked nasal blockage, discharge and pain are early manifestations of bacterial sinusitis. As the disease progresses the purulent discharge becomes profuse, thick and tenacious. The acute pain is replaced by a dull ache over the involved sinus or the pain may disappear entirely. Tenderness is often observed, while in children with ethmoid involvement, redness and swelling of the eyelids is apt to occur.

Inflammatory swelling of the membrane occludes the ostia early. Pus commonly can be traced to the ostium of the infected sinus, but if the swelling is severe it may be absent. Cultures are necessary not only to determine the responsible bacteria but also to guide treatment. As the disease continues, the inflammation diminishes, but pus persists and bone sclerosis or necrosis is often observed on the Roentgenogram.

In the early stages uncomplicated bacterial sinusitis resolves when the ostium is kept patent and care is taken not to damage the drainage mechanism. Conservative measures prevail, and after resolution has begun irrigations promote recovery.

Supplemental sulfonamide or penicillin therapy shortens the course of the infection, diminishes the number of complications, reduces the number of cases requiring surgery and, when surgery is needed, permits the use of less formidable surgical procedures. These drugs by combating the infecting organism in the early stages of the sinusitis eliminate the pathologic changes resulting from long-standing infection. Commonly, the causative organism belongs to the Gram positive group and is sensitive to penicillin. Better results are obtained when penicillin is given early, and infections from coagulase-positive staphylococci yield the best results.

In suppurative sinusitis of long duration both the bone and lining membrane become thickened, sclerotic and fibrotic, with dense scar tissue replacing the vascular membrane, and little permanent improvement can be expected from systemic sulfonamide or penicillin therapy even though susceptible organisms are present. Temporary improvement may be noted while the patient is receiving treatment, but symptoms return when it is discontinued.

After the pathologic change in the sinus membrane has become irreversible, some type of surgical treatment is required for relief of symptoms. Removal of the diseased bone or membrane can usually be accomplished without disturbing the normal tissues or function of the nose and adjacent sinuses. By using sulfadiazine or penicillin in conjunction with surgery, healing is more prompt, and more extensive procedures, such as are needed in cases of malignancy with complete exenteration of all sinuses on one side, can be carried out with little danger of osteomyelitis.

Complications of bacterial sinusitis are lessened and the mortality lowered by penicillin. In orbital cellulitis extensive surgery is rarely required, and regression occurs promptly after systemic penicillin therapy with vanishing pain after the first day of treatment. If pus forms, incision and drainage of the fluctuating area reduces the healing time.

Formerly, the dreaded complication of osteomyelitis was usually fatal when the frontal bone was involved. The mor-

tality was greatly reduced after Mosher[3] demonstrated that removal of all diseased bone by early radical surgery of the skull prevented meningitis and other grave intracranial extensions. Penicillin not only lessens the mortality but by eliminating or reducing the extent of operations also does away with the disfigurement of the surgical procedures formerly employed. In early osteomyelitis the vascular channels are prominent and numerous, and resolution is prompt under penicillin; if pus is present, incision and drainage promote recovery. Penicillin does not supplant surgical procedures in chronic osteomyelitis but helps materially in combating the disease and renders any surgical procedure safer. In chronic osteomyelitis the infection can be controlled and the wounds sterilized while the patient is receiving penicillin, but on discontinuing the drug the infection again becomes active. Putney[4] reported that surgical drainage, which often includes radical sinus surgery, is necessary in addition to penicillin therapy to cure many of these chronic cases. Even though penicillin controls the osteomyelitic process, the primary infection in the sinus may demand surgery. Adequate, lengthy and repeated courses of penicillin are given before surgical intervention, but the latter is required if the disease fails to heal.

SUMMARY.

Realization of the importance of proper nasal and sinus physiology alters the approach to the problem of sinusitis, while the antibiotic and chemotherapeutic agents afford valuable weapons in treatment. Restoration rather than destruction of diseased tissue is the cardinal aim. When the pathologic change in the membrane is irreversible surgery is required, conservative operations being preferred. In long-standing suppurative sinusitis the membrane becomes fibrotic and little benefit results from the sulfonamides or penicillin. Sinusitis is classified as follows: *1.* allergic, *2.* mechanical, *3.* bacterial. In general, allergic cases require primary attention to the allergic diathesis, those due to mechanical blockage are relieved by simple surgical procedures, and early

bacterial sinusitis responds to penicillin. Penicillin is equally valuable in treating the complications of orbital cellulitis and osteomyelitis of the skull. When given early surgery can often be avoided, but in chronic osteomyelitis surgical drainage is usually needed in addition.

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THE AMERICAN OTORHINOLOGIC SOCIETY FOR THE ADVANCEMENT OF PLASTIC AND RECONSTRUCTIVE SURGERY, INC.

The next meeting of the American Otorhinologic Society for the Advancement of Plastic and Reconstructive Surgery will be held at the New York Academy of Medicine Building, New York City, Thursday, Nov. 13, 1947, at 8:00 P.M. Programs are available through the Secretary.

A dinner will precede the meeting at 6:00 P.M. at Hotel Plaza. Reservations may be made with Dr. Norman N. Smith, Secretary, 291 Whitney Avenue, New Haven, Conn.

PLASMOCYTOMA: REPORT OF A CASE.*

JAMES B. COSTEN, M.D.,
St. Louis, Mo.

A single case of plasmocytoma is the basis for this report, the primary tumor having been found on the base of the tongue, on the right side, with one adjacent lymph node found with the tumor. It occurred in a 60-year-old male, in good general health and carrying on his work, in a light occupation, in spite of evidence of the spread of the tumor to several areas in the pelvis. Eradication of the original focus of the tumor was done by cautery removal; the adjacent glands were removed and interstitial radiation made by means of radon seeds within the base of the tongue, and the cervical region around the angle of the jaw. At this date, one year later, there is no evidence of local recurrence.

The case belongs to the extramedullary group of plasma cell myelomas, the original lesion of most of which is found to occur in some area of the upper respiratory tract. Plasmocytoma was considered by earlier observers to be a granuloma associated with chronic inflammation, because of the association of the plasma cell within such reactions. Careful study of the typical cases selected from large groups of tumors about the head and neck shows plasmocytoma to be a true tumor with tendency to metastasize, but slowly. Jackson, Parker and Bethea[1] made careful studies of 17 cases of myeloma, and described the relationship of plasmocytoma. Clayborne and Ferris[2] reviewed the literature previous to 1931, and found only 12 cases, to which two of their own were added. The largest classified group of malignant tumors, exclusive of adenocarcinoma and found about areas of the pharynx, were presented by New and Childrey,[3] in 1931. Out of 357 cases, two were found to be plasmocytoma. One year later, New and Harper[4] presented a specific study of plasma cell myeloma, occurring about the pharynx and cervical re-

*Read at the Fifty-first Annual Meeting of the American Laryngological, Rhinological and Otological Society, Inc., St. Louis, Mo., April 25, 1947.

gion. The next important report appeared in June, 1945, in which Figi, Broders and Havens[3] presented 11 cases of plasma cell myeloma, the original lesions of which were found in the upper part of the respiratory tract, describing all such cases which had been seen in the Mayo Clinic in a period of 14 years from 1930 to 1943, inclusive. One was a duplication of a case previously reported by New and Harper.[4] The case reported below shows no disability resulting from distant metastases, even though there is X-ray evidence of such metastases in the ilia. This patient has been under observation one year, and it is assumed that the lesion at the base of the tongue next to the lower pole of the right tonsil was the primary focus of the tumor.

Case 1: A 60-year-old male, first examined April 27, 1946, complaining of a lump in the throat, which had been present about three months and seemed to have rapidly increased in size the previous two months. His appetite was good, his weight stationary, and he had had no other symptoms outside of the throat obstruction. In his past history, he was said to have had a fractured right hip in 1930, with good recovery, and osteomyelitis of the right rib in 1940, operated on and recovered. Local examination showed a round mass, dark bluish red in color, about 2.5 cm. in diameter, protruding from a broad base, attached at the lower right border of the tongue, and lower pole of the right tonsil. The nasal pharynx was free of any mass, as was the hypopharyngeal spaces. At the right angle of the jaw was a firm mass which was freely movable beneath the skin, but deeply attached, rounded on the surface and about the size of a small olive. No other cervical masses observed. All other physical findings were entirely negative. Under local anesthesia, a liberal piece of the original tumor was removed for biopsy. This section was examined by Dr. George Ives, diagnosed plasmocytoma, and the patient was admitted to McMillan Hospital on May 1, 1946.

On May 2, 1946, the tumor was removed from the base of the tongue, by clamping the broad pedicle and incising along this clamp with actual cautery. There was only slight bleeding. After this was controlled, seven radon seeds, 1.5 millicuries each, were introduced deeply into the zone surrounding the origin of the tumor, five into the tongue and two into the lower pole of the right tonsil. Three similar seeds were passed through the skin, externally, to the region of the tumor, around the angle of the jaw. On May 15, 1946, the large gland was removed under local anesthesia, together with all regional glands which could be identified. The largest was reported from the Department of Pathology as plasmocytoma, metastatic in the lymph nodes. None of the remaining smaller glands contained the tumor.

Several blood counts were made, and all cells were within normal limits; platelets appeared normal, and no plasma cells were seen. The Schilling differential counts were within normal limits. No Bence-Jones proteinuria was found, several specimens being examined during the recuperation period. Chest film made on May 22, 1946, showed aortic lengthening, bronchial infiltration and fibrosis of an indeterminate nature, calcified pleura, right side, and old pleurisy, both bases. Complete Roentgenographic study was made of all the skeletal structures. Skull,

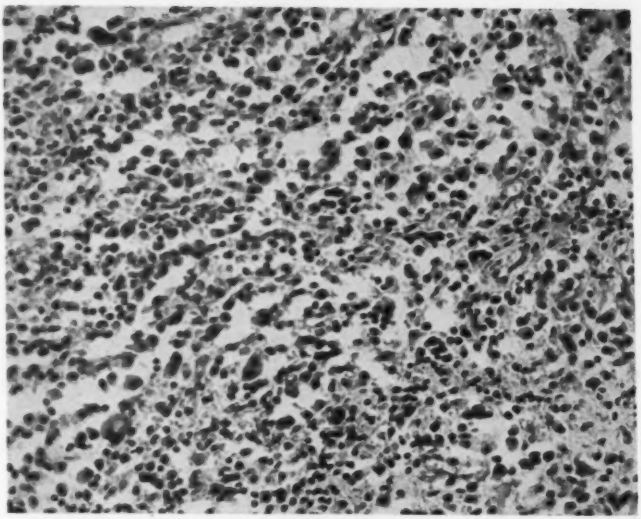

Fig. 1.

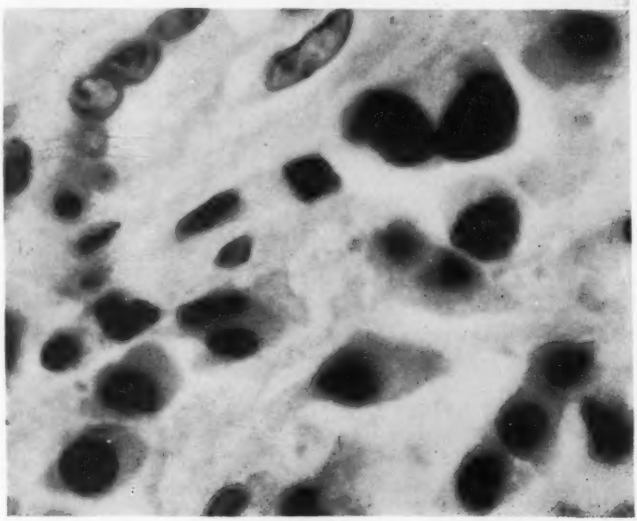

Fig. 2.

cervical spine and long bones were entirely clear. In the left ilium, however, there were numerous ovoid areas of rarefaction and several smaller ones in the right ilium. These were given a diagnosis of metastatic carcinoma. The patient was discharged from hospital on May 22, 1946.

"The substance of the tissue is made up of a characteristic cell. This cell is of the plasma cell variety, being characterized by ovoid, abundant, faintly eosinophilic cytoplasm with an eccentric round hyperchromatic nucleus with some tendency of the nuclear-chromatin to clump in the form of the characteristic spoke-wheel arrangement. There is a slight perinuclear clear zone. Many of the cells have two nuclei,

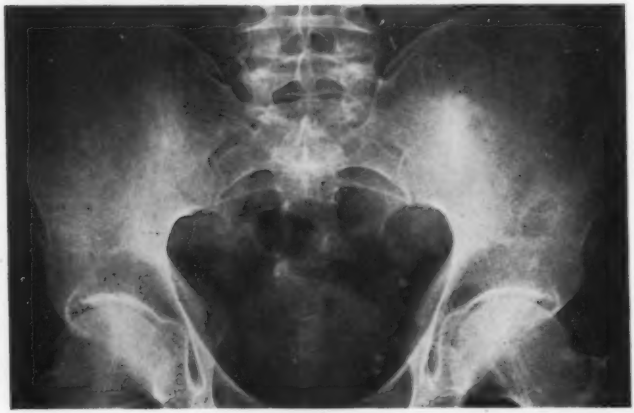

Fig. 3.

others have three or even four nuclei. In these latter cells, the cytoplasmic elements are smaller in proportion to the size of the nuclei than in the typical plasma cell types. There is very little stroma associated with the cells; however, in some areas, there is an infiltration with leucocytes and fibrin.

"*Diagnosis:* Plasmocytoma.

Robert A. Moore, M.D.,
Professor of Pathology, Washington University School of Medicine."

Comment: The case appears to be one of typical plasmocytoma, with mild degree of malignancy, no local symptoms having resulted from the metastatic lesions in the pelvis to date. Recent specimens have shown no Bence-Jones proteinuria, and the roentgenographic study of all bone structures has not been repeated for one year. He seems to be in the long quiet phase, which occurs between the removal of the original tumor and the generalized spread which affects the bony structures in the terminal phases. The question has been raised, whether or not his earlier pathology in the rib and hip fracture which could have been related to tumor formations, but no local evidence of tumor in these areas can be shown.

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BOOK REVIEW.

Hearing Aids; An Experimental Study of Design Objectives. By Hallowell Davis (with six other members of the staffs of Psycho-Acoustic and Electro-Acoustic Laboratories, Harvard University). Cambridge, Mass., Harvard University Press, 1947. 197 pages.

The original purpose of the experiments reported in this study was to provide appropriate design objectives for the construction of hearing aids and to develop clinical methods to determine the pattern of frequency response which would best compensate each individual hearing loss.

The first purpose is reported as achieved through experimentation on a group of 18 hard-of-hearing men and women ranging in age from 17 to 70 years, with varying degrees and representative types of deafness. Articulation functions were run for the subjects on a master hearing aid. This instrument was designed to provide a choice of five simple frequency characteristics clearly distinct from one another in slope. The basic frequency characteristic of the master hearing aid was "flat" $\pm$ 3 db. from 100 to 3,000 c.p.s. and $\pm$ 5 db. from 100 to 7,000 c.p.s. The spectrum could also be "tilted" upwards or downwards to attain a uniform rise of either 6 db. or 12 db. per octave. Maximum acoustic output was limited by simple symmetrical peak clipping at selected levels. The major specifications recommended are:

"Frequency Response and Range.—Uniform, i.e., without marked resonant peaks or valleys, from 300 to 4,000 c.p.s. Sharp cutoffs below and above this range are desirable. The one best frequency characteristic is a moderate high-tone emphasis of from 4 to 6 db. per octave over this range.

"Tone Control.—It is desirable to provide a selection between a flat, a rising 3 db. and a rising 6 db. per octave frequency characteristic.

"Limiting of Output.—Preferably by compression amplification; alternatively by simple symmetrical peak clipping.

"Maximum Output.—Semipermanent adjustment, or provision of separate models, at 114, 120, 126 or 132 db. re 0.0002 dyne/cm.^{2} maximum instantaneous acoustic pressure.

"Maximum Acoustic Gain.—Separate models would probably be desirable, the lowest powered to have at least 40 db. acoustic gain available, the highest powered a maximum of 80 db.

"Gain Control.—Smoothly graded or in small steps on an approximately logarithmic scale over a 40 db. range.

"Intrinsic Noise.—Must not mask speech delivered to the instrument at a sound-pressure level of 30 db."

The experimentation involved in attaining the first purpose showed that the "fitting" of hearing aids should be based primarily on the maximum acoustic output required by the wearer. "Fitting" should not be based on the relation between the frequency characteristic of the instrument and the "shape" of the patient's audiogram. Appropriate high-tone emphasis could be achieved through adjustment of the tone control.

This report challenges some long cherished concepts of "fitting" hearing aids and it will be interesting to watch the results of clinical application of the basic principles based on laboratory findings. Such application is now in progress in some hearing clinics. S. R. S.

HEARING AIDS ACCEPTED BY THE COUNCIL ON PHYSICAL MEDICINE OF THE AMERICAN MEDICAL ASSOCIATION.

Aurex (Semi-Portable); Aurex Model C-B and Model C-A.

Manufacturer: Aurex Corp., 1117 N. Franklin St., Chicago, Ill.

Beltone Mono-Pac; Beltone Harmony Mono-Pac.

Manufacturer: Beltone Hearing Aid Co., 1450 W. 19th St., Chicago, Ill.

Maico Type K; Maico Atomeer.

Manufacturer: Maico Co., Inc., North Third St., Minneapolis, Minn.

Mears Aurophone Model 98.

Manufacturer: Mears Radio Hearing Device Corp., 1 W. 34th St., New York, N. Y.

Otarion Model A-1; Otarion Model A-2; Otarion Model A-3; Otarion Model A-4 Jr.

Manufacturer: Otarion Hearing Aids, 448 N. Wells St., Chicago, Ill.

Paravox Models VV2 and VV3; Paravox Models VH and VL; Paravox Model XT.

Manufacturer: Paraphone Hearing Aid Co., 2056 E. 4th St., Cleveland, Ohio.

Radioear Masterpiece; Radioear 45-CM; Radioear Model 45-M-magnetic air conduction receiver; Radioear Model 45-M-magnetic bone conduction receiver.

Manufacturer: E. A. Myers & Sons, 306 Beverly Rd., Mt. Lebanon, Pittsburgh, Pa.

Silver Micronic Hearing Aid.

Manufacturer: Micronic Corp., 101 Tremont St., Boston 8, Mass.

Ravox (Semi-Portable).

Manufacturer: Zenith Radio Corp., 6001 W. Dickens Ave., Chicago, Ill.

Sonotone Audicles No. 530, No. 531 and No. 533; Sonotone Model 600; Sonotone Model 700.

Manufacturer: Sonotone Corp., Elmsford, N. Y.

Telex Model 22; Telex Model 612; Telex Model 900; Telex Model 1020; Telex Model 1550.

Manufacturer: Telex, Inc., Minneapolis 1, Minn.

Trimm Vacuum Tube No. 300.

Manufacturer: Trimm, Inc., 400 W. Lake St., Libertyville, Ill.

Unex Model "A."

Manufacturer: Nichols & Clark, Hathorne, Mass.

Vacolite Model D.

Manufacturer: Vacolite Co., 3003 N. Henderson, Dallas, Tex.

Western Electric Audiophone Ortho-technic Model; Western Electric Telephone Type Audiophone Model J-1; Western Electric Model 63; Western Electric Model 64.

Manufacturer: Western Electric Co., Inc., 300 Central Ave., Kearny, N. J.

Zenith Radionic Model A-2-A; Zenith Radionic Model A-3-A; Zenith Radionic Model B-3-A.

Manufacturer: Zenith Radio Corp., 6001 Dickens Ave., Chicago, Ill.

NATIONAL HEARING WEEK, NOV. 9-15, 1947.

With 3,000,000 children in the United States having a hearing loss, and millions of adults already hard of hearing, it is time to conserve hearing, according to Dr. C. Stewart Nash, President of the American Hearing Society, Washington, D. C. The national organization is joined by its 120 local chapters throughout the country in the observance of National Hearing Week, Nov. 9-15.

"Authorities estimate that one out of every 10 persons in America has a hearing loss, ranging from a slight loss to almost total deafness. The social and mental effects of this hearing loss can do much to warp the personality of a growing child and in addition may prove an effective bar to the child's making a success of later life," said Dr. Nash. He stressed the necessity for parents and teachers to watch children carefully for any signs of hearing loss, especially after illnesses involving the nasal passages, ears or throat.

"Prompt attention by a competent otologist is necessary where such a hearing loss is suspected," Dr. Nash declared. "Inattention, falling grades in school, a tendency to shun the company of other persons are often indications of a beginning hearing loss. The majority of people with serious hearing defects need never have reached that stage if the trouble had been checked in its incipient state."

Dr. Nash recommended a vigorous hearing conservation program to be put in effect in the school system of the nation. This includes periodic hearing tests, medical examinations followed by prompt medical attention, if any impairment is discovered, and adequate education and rehabilitation for those with a handicapping hearing loss.

THE AMERICAN LARYNGOLOGICAL, RHINOLOGICAL AND OTOLOGICAL SOCIETY, INC.

The coming Section Meetings will be held as follows:

Eastern Section—Jan. 16, 1948.....New York, N. Y.

Middle Section—Jan. 19, 1948.....Columbus, Ohio

Southern Section—Jan. 23, 1948.....New Orleans, La.

Western Section—Jan. 31-Feb. 1.....San Francisco, Calif.

(The mid-winter Council Meeting will be held in New York, N. Y., on Jan. 17, 1948.)

Arrangements have been made to hold the Annual Meeting at Chalfonte-Haddon Hall in Atlantic City on April 7, 8 and 9, 1948. The mornings will be devoted to scientific sessions; the afternoons will be left free.

The American Otological Society and the American Laryngological Association are planning to hold their meetings at Old Homestead, Va.—the former on April 12 and 13, 1948; the latter on April 14 and 15, 1948.

This plan to have a three-day Triological meeting with free afternoons and an interval of two days between the Atlantic City and the Old Homestead meetings is projected in order to relieve the strain of concentrating within one week the combined activities of these three societies. Address any inquiries to Dr. C. Stewart Nash, Secretary.

DIRECTORY OF NATIONAL OTOLARYNGOLOGIC SOCIETIES.

AMERICAN OTOLOGICAL SOCIETY.

President: Dr. Bernard J. McMahon, 806 Missouri Theatre Bldg., St. Louis 3, Mo.
Secretary: Dr. Gordon D. Hoople, Medical Arts Bldg., Syracuse 3, N. Y.
Meeting: Hot Springs, Va., The Homestead, April 14-15, 1948.

AMERICAN LARYNGOLOGICAL ASSOCIATION.

President: Dr. Arthur W. Proetz, Beaumont Bldg., St. Louis 8, Mo.
Secretary: Louis H. Clerf, 1530 Locust St., Philadelphia 2, Pa.
Meeting: Hot Springs, Va., The Homestead, April 14-15, 1948.

AMERICAN LARYNGOLOGICAL, RHINOLOGICAL AND OTOLOGICAL SOCIETY, INC.

President: Dr. Lyman G. Richards, 15 Whiting Road, Wellesley Hills, Mass.
Secretary: Dr. C. Stewart Nash, 708 Medical Arts Building, Rochester, N. Y.
Meeting: Atlantic City, N. J., Chalfonte-Haddon Hall, April 7-9, 1948.

SECTIONS:

Eastern—Chairman: Dr. J. Winston Fowlkes, New York, N. Y.
Meeting: New York, N. Y., Jan. 16, 1948.

Middle—Chairman: Dr. Hugh G. Beatty, Columbus, Ohio.
Meeting: Columbus, Ohio, Jan. 19, 1948.

Southern—Chairman: Dr. William A. Wagner, New Orleans, La.
Meeting: New Orleans, La., Jan. 23, 1948.

Western—Chairman: Dr. Meade Mohun, San Mateo, Calif.
Meeting: San Francisco, Calif., Jan. 31-Feb. 1, 1948.

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Secretary: Dr. Fletcher D. Woodward, 104 E. Market Street, Charlottesville, Va.

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LOS ANGELES SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

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Vice-President: Dr. Leland G. Hunnicutt.
Secretary-Treasurer: Dr. K. C. Brandenburg.
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Meeting: Los Angeles County Medical Association Building, 1925 Wilshire Boulevard, Los Angeles, Cal.
Time: 6:00 P.M., fourth Monday of each month from September to May, inclusive.

AMERICAN OTORHINOLOGIC SOCIETY FOR THE ADVANCEMENT OF PLASTIC AND RECONSTRUCTIVE SURGERY.

President: Dr. Alfred Schattner, 115 E. 61st Street, New York 21, N. Y.
Secretary: Dr. Norman N. Smith, 291 Whitney Avenue, New Haven 11, Conn.
Meeting: New York City, New York Academy of Medicine, Nov. 17, 1947.

SOUTHERN MEDICAL ASSOCIATION, SECTION ON OPHTHALMOLOGY AND OTOLARYNGOLOGY.

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